Immunomodulatory treatment trial for paraneoplastic neurological disorders

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Paraneoplastic neurological disorders are devastating remote effects of malignancy. Despite compelling evidence of an autoimmune pathogenesis, empiric immunomodulatory treatment of these disorders is often ineffective. However, very few systematic studies have been conducted, and the treatment of patients without active malignancy has not been addressed. We conducted a prospective open-label treatment study of plasma exchange plus conventional cancer chemotherapy (10 patients) or plasma exchange plus continuous oral cyclophosphamide (10 patients). All patients had progressive symptoms and at least moderate disability at enrollment (mean Rankin score, 3.4). Patients who had experienced symptoms for more than 12 months were excluded (mean duration of symptoms at enrollment, 3.6 months). The primary outcome measure was change in quantitative disability measures (Rankin and Barthel scores) after 6 months of treatment; a positive response was defined as stability or improvement in disability. Overall, 50% of patients had a positive response at 6 months (6 patients had improved by at least 1 Rankin grade). Patients with good outcome tended to be those with less disability at time of enrollment. Hematologic toxicity was common among those receiving cyclophosphamide. Aggressive immunosuppression early in the clinical course should be considered in patients who have paraneoplastic neurological disorders, even when there is no evidence of active malignancy. *Neuro-Oncology 6, 55–62, 2004 (Posted to Neuro-Oncology [serial online], Doc. 03-039, November 21, 2003. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152 8517 03 00039 5*

Neurologic paraneoplastic syndromes represent a rare but severe neuroimmunological complication of malignancy (most commonly, small-cell lung carcinoma and ovarian carcinoma). Clinical manifestations can be quite varied and multifocal in the nervous system. Several distinct clinical syndromes are recognized, including sensory neuronopathy, cerebellar degeneration, limbic encephalitis, and opsoclonus-myoclonus. These disorders are usually associated with a subacute onset and significant disability (Graus et al., 2001). In paraneoplastic cerebellar degeneration, for example, more than 90% of patients become nonambulatory (Rojas et al., 2000). Spontaneous improvement has been reported but is distinctly unusual. Typically, the neurologic presentation antedates the diagnosis of malignancy, and the cancer, when found, tends to be localized and responsive to treatment (Graus et al., 1997).

Neuron-specific autoantibodies are often found in the serum and cerebrospinal fluid of these patients. Except in the cases of Lambert-Eaton myasthenic syndrome and autoimmune myasthenia gravis, these antibodies are not considered pathogenic. Many of the antibodies are specific for nuclear or cytoplasmic antigens that are probably not accessible to extracellular immunoglobulin (Lennon, 1994).

While paraneoplastic autoantibodies may not be pathogenic and do not always correlate with particular neurologic syndromes, they are highly specific for the presence of occult malignancy and are predictive of the tumor type. These immunoglobulin G (IgG)[2] autoantibodies serve as surrogate markers of a specific T-cell immune

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[2] Abbreviations used are as follows: ADL, activities of daily living; IgG, immunoglobulin G; ivIg, intravenous immunoglobulin; PLEX, plasma exchange; RS, Rankin score.

response. Neuron-specific IgGs reactive with cytoplasmic and nuclear antigens may be accompanied by activated $CD8^+$ cytotoxic T cells specific for immunodominant peptides derived from intracellular antigens (Albert et al., 1998, 2000). Cellular autoimmunity is probably the critical mediator of neuronal damage in paraneoplastic neurological syndromes.

Despite our improving understanding of the pathogenesis of these disorders, it is generally thought that immunomodulatory treatment is ineffective (Dalmau and Posner, 1997; Jaeckle, 1996) and that treatment of the underlying malignancy is the only available treatment for these disorders (Bataller et al., 2001; Dropcho, 1995; Graus et al., 1992, 2001). The treatment of patients who do not have evidence of an active malignancy, however, has never been studied specifically. Information on treatment response is largely based on retrospective series in which a variety of treatments were used in an uncontrolled fashion. In one review of available retrospective case series (Grisold et al., 1995), only 33 cases of effective treatment were documented out of 259 reported cases.

A few systematic case series have been reported. Two studies have been reported that used intravenous immunoglobulin (ivIg) or ivIg in combination with pulse intravenous cyclophosphamide and methylprednisolone (Keime-Guibert et al., 2000; Uchuya et al., 1996). Treatment, however, was given for a variable duration and in combination with chemotherapy in many cases. Among patients with progressive neurological disease, 35% to 40% of patients stabilized neurologically, and only 1 patient improved. The authors concluded that this immunomodulatory treatment was not useful for patients with severe disability but may provide a useful stabilization of disability in patients who are still ambulatory (Keime-Guibert et al., 2000).

In contrast, there have been numerous individual case reports of neurological improvement using corticosteroids (Oh et al., 1997), ivIg (Blaes et al., 1999; Counsell et al., 1994; David et al., 1996; Glantz et al., 1994; Guy and Aptsiauri, 1999; Moll et al., 1993; Mowzoon and Bradley, 2000; Oh et al., 1997), plasma exchange (PLEX) (Cocconi et al., 1985; David et al., 1996; Rickman et al., 2000; Weissman and Gottschall, 1989), or cyclophosphamide (Batson et al., 1992; Bruyland et al., 1984; Faris et al., 1998; Mowzoon and Bradley, 2000; Oh et al., 1991; Schmierer et al., 1998; Stark et al., 1995). In addition, at least partial or temporary improvement in neurological deficits was reported in 75% of patients treated with immunoadsorption therapy in a prospective treatment protocol (Batchelor et al., 1998). In many instances, patients who responded were treated within a few weeks of neurological symptom onset, which suggests that treatment should be instituted early in the clinical course. Results of some studies also indicate that syndromes limited to the peripheral nervous system are more likely to respond than those affecting the CNS (Keime-Guibert et al., 2000; Uchuya et al., 1996).

Clearly, systematic prospective treatment trials with predefined end points are needed. These studies should include quantitative measures of neurological disability and assessment of durability of the oncological and neurological response. Based on the available literature, we organized a single-center, prospective, open-label (phase 2) trial. This study was designed to evaluate the efficacy of an acute treatment (PLEX) combined with either chemotherapeutic cancer treatment or immunosuppression (oral cyclophosphamide).

Methods

Study Design

The study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB #2041-99). The primary study end point was change in disability at 6 months as assessed by modified Rankin scale (Rankin, 1957) and Barthel index (Mahoney and Barthel, 1965) scores. Treatment success was defined as stability or improvement in disability. Improvement was defined as any improvement in Rankin score (RS) or a 10-point increase in Barthel functional index. Worsening was defined as any worsening of RS or a 10-point decline in Barthel index. Patients who neither improved nor worsened were classified as stable. Secondary end points were survival, paraneoplastic antibody titer, adverse events, and oncological status.

A 2-stage Fleming design was applied separately to each treatment arm in order to permit accrual to be stopped early for unusually good results as well as for discouraging results. This 0.10-level test of the null hypothesis (true treatment success probability $\leqslant$10%) had 90% power to detect a true "success" probability of $\geqslant$40%. In the first stage, accrual into each treatment arm was suspended after 10 patients had been enrolled in that arm. Accrual of an additional 5 patients was required only if exactly 2 treatment successes were observed in the first 10 patients enrolled in that study arm. The second enrollment stage was not required for either of the treatment groups.

The "success" probability in each study arm was estimated by using the standard binomial point and 90% confidence interval estimators. Summary statistics were calculated for all clinical variables. For categorical variables, the exact chi-squared test was used to compare distributions. For continuous variables, exact Wilcoxon rank-sum tests were used to investigate differences in the distributions between subsets of patients classified by categorical data (i.e., outcome or treatment arm assignment). The Kaplan-Meier method was used to estimate survival, defined as the time between study registration and death. Because the number of patients enrolled was small, this study has limited power to detect definite statistical significance (defined as $P < 0.05$). All P-values are reported to facilitate the identification of trends in the data.

Patient Selection

Patients were identified through referral to the first author from their attending oncologists or neurologists. Patients were considered for enrollment if they had a neurological syndrome (other than myasthenia gravis or Lambert-

Eaton syndrome) that was temporally correlated with the diagnosis of solid malignancy or with the identification of an established paraneoplastic antineuronal autoantibody. Patients with nervous system metastases, unstable general medical conditions (e.g., sepsis, renal failure), and those with hematological malignancies (lymphoma, leukemia, or myeloma) were not considered. All patients completed neurological examination, cancer screening (including body CT), cranial MRI, and laboratory studies prior to enrollment. To facilitate detection of changes in functional status, bedridden patients (RS = 5) and patients with minimal disability (RS = 1) were excluded. We also excluded patients who had experienced neurological symptoms for more than 1 year and those who were not subjectively worsening at the time of assessment. We used these criteria to exclude patients who were neurologically stable, those with chronic indolent disease, and those with long-standing (probably irreversible) neurological deficits. Other exclusion criteria are listed in Table 1. All patients provided written informed consent prior to starting treatment.

Treatment

Prior to enrollment, all patients were evaluated by an oncologist to confirm the adequacy of cancer screening, to assess the status of a known malignancy, and to recommend appropriate cancer treatment. Following the oncological recommendations, patients were assigned to 1 of 2 treatment arms. Patients who did not require cancer chemotherapy were assigned to treatment arm A. This arm included patients with no evidence of active malignancy who were seropositive for paraneoplastic antibodies as well as patients with known cancer that did not require chemotherapy. Patients in treatment arm A received PLEX followed by oral cyclophosphamide (initial dose of 2 mg/kg/day in divided doses). All patients in arm A were instructed to increase fluid intake to reduce the risk of hemorrhagic cystitis. Patients who required cancer chemotherapy were assigned to arm B and received PLEX followed by standard cytotoxic chemotherapy under the direction of their oncologist. In both arms, PLEX was performed every other day for a total of 5 exchanges. In each exchange, 1 plasma volume (estimated from height and weight; 2500–4000 ml) was removed by centrifugation apheresis and replaced with 5% albumin and normal saline. During 2001, because of a national shortage of albumin, many patients also received 500 ml of 6% hetastarch to reduce the volume of albumin required for each exchange. Chemotherapy or oral cyclophosphamide was initiated within 2 days of completion of PLEX treatments. Physical, occupational, or speech therapy was provided as appropriate to the clinical situation.

Table 1. Exclusion criteria

Exclusion criteria	No. of patients excluded
Neurologic symptoms stable or improving at time of evaluation	2
Duration of neurological symptoms >12 months	7
Rankin disability score <2 or >4	3
Age <18 years	0
Abnormal laboratory values *	3
Leukocytes <3400/mm^3	
Platelets <100,000/mm^3	
Hemoglobin <10 g/dl	
Serum AST >3 x upper limit of normal	
Creatinine >1.5 x upper limit of normal	
Pregnancy	0
Refuses treatment	1

The abbreviation used is as follows: AST, serum glutamic oxaloacetic transaminase.

* Initial laboratory studies performed within 14 days of enrollment.

Evaluation

Patients were evaluated for disability at 3 months and at 6 months following initiation of treatment. Neurological disability was quantified by using a modified Rankin scale (Rankin, 1957) and the Barthel functional index (Mahoney and Barthel, 1965). The RS ranges from 1 to 6 (1, able to carry out all usual activities of daily living [ADLs] without any assistance; 2, slight disability—able to care for self without much assistance; 3, requires help with ADLs but able to walk without assistance; 4, requires assistance to stand and walk but able to participate in some ADLs; 5, severe disability—bedridden or requiring constant nursing care and attention; 6, dead). The Barthel index assesses independence of basic self care (including feeding, grooming, toilet, bathing, walking, dressing). A score of 100 indicates complete independence in basic ADLs, and a score less than 70 reflects significant dependence. The Barthel index is less dependent on ambulation and therefore complements the RS.

Laboratory monitoring with complete blood count, liver enzymes, and urine microscopy was performed at 2-week intervals for patients in arm A. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI, 1999). The dose of cyclophosphamide was decreased if grade 2 cytopenia was documented and discontinued if grade 3 or 4 neutropenia developed. In arm B, monitoring for toxicity was performed by the attending oncologist.

For seropositive patients, serum paraneoplastic antibody titers were determined by serial titration in a standardized immunofluorescence assay at the Mayo Clinic Neuroimmunology Laboratory (Lennon, 1994). Telephone or clinical follow-up was continued indefinitely following completion of the study.

Results

Patient Characteristics

Between February 2000 and April 2002, 36 patients were considered for enrollment. Sixteen were excluded (Table 1). Twenty patients (5 men; 15 women) were

Table 2. Clinical features of patients treated for paraneoplastic neurological disorder

					CSF[†]			Initial			
Arm-Pt.	Age Sex	Cancer	Syndrome	Duration (mo)	Protein (mg/dl)	Cells	Antibody	Ab titer[‡]	RS	Barthel	ChemoTx
A-1	60/M	None[1]	PLE Gastro-paresis	6	61	2	ANNA-1	3,840	2	95	CYT 20 mos
A-2	36/M	Thymoma	PLE	9.5	180	1	None	—	2	85	CYT 9 mos
A-3	55/F	Ovarian	PCD	0.5	ND	ND	PCA-1	1,920	3	95	CYT 30 mos
A-4	78/F	SCLC	PSN	4.5	ND	ND	ANNA-1	15,360	2	90	CYT [2] 2 mos
A-5	71/F	None	Ataxia, optic neuropathy	3.5	105	2	CRMP-5	960	3	85	CYT 8 mos
A-6	55/F	Ovarian	PCD	0.5	56	50	PCA-1	3,840	3	55	CYT [2] 3 mos
A-7	72/F	Ovarian	PCD	1	83	7	PCA-1	122,880	3	80	CYT [2, 3] 4 mos
A-8	74/F	Fallopian	PCD	1	60	7	PCA-1	7,680	4	40	CYT [2, 3] 2 mos
A-9	53/F	Ovarian	Motor neuropathy	8.5	97	57	PCA-1	3,840	4	25	CYT [4] 1 mo
A-10	73/M	TCC	Ataxia, encephalitis	3	186	44	None	—	4	25	None
B-1	63/M	SCLC	PSN	3.5	135	22	ANNA-1	7,680	3	85	Etoposide Carboplatin
B-2	57/F	Breast	PCD	5.5	49	1	None	—	4	45	Doxorubicin CYT
B-3	46/F	Peritoneal	PCD	1	ND	ND	PCA-1	122,880	4	25	Paclitaxel Carboplatin
B-4	39/F	Ovarian	PCD	7.5	ND	ND	PCA-1	15,360	4	45	Doxorubicin[5]
B-5	60/F	Ovarian	PCD	1.5	84	12	PCA-1	122,880	4	65	Paclitaxel Carboplatin
B-6	56/F	Ovarian	PCD	5	75	21	PCA-1	15,360	4	40	Paclitaxel Carboplatin
B-7	65/F	Endometrial	PCD	1	ND	ND	PCA-1	61,440	3	95	Doxorubicin CYT
B-8	71/M	SCLC	PLE, PSN	1.5	ND	ND	ANNA-1	61,440	4	75	Etoposide Carboplatin
B-9	66/F	Ovarian	PCD	5.5	64	0	PCA-1	960	4	60	Paclitaxel Carboplatin
B-10	57/F	SCLC	Encephalitis	2.5	79	1	ANNA-1	7,680	4	30	None

Abbreviations used are as follows: Ab, antibody; ANNA-1, antineuronal nuclear antibody, type 1; ChemoTx, chemotherapy; CR, cancer in remission; CRMP-5, collapsin-response mediator protein antibody; CSF, cerebrospinal fluid; CYT, cyclophosphamide; f/u, follow-up; ND, not done; PCA-1, Purkinje cell antibody, type 1; PCD, paraneoplastic cerebellar degeneration; PLE, paraneoplastic limbic encephalitis; PSN, paraneoplastic sensory neuropathy; RS, Rankin score; SCLC, small-cell lung carcinoma; TCC, transitional cell carcinoma.

[†] CSF analysis. Normal values: protein 0-45 mg/dl, cells (nucleated cells per microliter) <5.

[‡] Antibody titers are the reciprocal of the highest dilution yielding a positive result by immunofluorescence assay.

[1] Non-small-cell lung carcinoma diagnosed after completion of study, 32 months after symptom onset.

[2] CYT discontinued because of persistent leukopenia despite dose reduction.

[3] Subsequently continued on oral mycophenolate mofetil without improvement.

[4] Oral CYT discontinued because of intractable nausea; continued with monthly intravenous CYT treatments.

[5] Patient elected to discontinue chemotherapy after 1 cycle. Lost to follow-up after 6-month assessment.

enrolled (Table 2). Ten patients received PLEX followed by daily oral cyclophosphamide (arm A), and 10 received PLEX followed by conventional chemotherapy given intravenously at 3- to 4-week intervals (arm B). Table 3, which summarizes the patients' baseline characteristics, shows that the patients in arm B tended to be younger and have more severe disability at baseline (higher RS and lower Barthel index). These differences were not statistically significant, however.

Overall, 11 patients had Purkinje cell antibody, type 1 (also known as PCA-1 or anti-Yo); 5 patients had antineuronal nuclear antibody, type 1 (also known as ANNA-1 or anti-Hu); and 1 patient had collapsin-response mediator protein antibody (also known as

Table 2. Continued

6 months					
Ab titer‡	RS	Barthel	Outcome	Cancer Status	Last f/u (mo)
960	1	100	Improved	CR	41, alive
—	1	100	Improved	CR	29, alive
240	2	100	Improved	CR	38, alive
7,680	2	100	Improved	CR	36, alive
960	3	95	Improved	—	31, alive
3,840	3	95	Improved	CR	30, dead
ND	4	55	Worse	Active	24, alive
15,360	5	15	Worse	CR	25, alive
7,680	5	10	Worse	CR	14, dead
ND	6	0	Worse	—	0, dead
3,840	2	90	Improved	CR	25, alive
—	3	80	Improved	CR	27, alive
1,920	3	65	Improved	CR	34, alive
ND	4	45	Stable	Active	23, alive
61,440	4	35	Worse	CR	29, alive
3,840	4	20	Worse	CR	30, alive
7,680	4	70	Worse	CR	25, alive
ND	6	0	Worse	—	2, dead
ND	6	0	Worse	—	2, dead
ND	6	0	Worse	—	1, dead

CRMP-5-IgG or anti-CV2). Three patients had cancer without a detectable paraneoplastic antibody marker. Seven patients were known to have cancer prior to the onset on their neurological syndrome. Among the others, the median delay from neurological symptom onset to cancer diagnosis was 3.5 months (range, 1–32 months), and 1 patient has not had cancer diagnosed through 29 months of follow-up. There were 8 patients with ovarian carcinoma and 3 with other pelvic intraperitoneal carcinomas, 4 with small-cell lung carcinoma, and 4 with other tumors.

Neurological Outcome

Overall, treatment success (stabilization or improvement in disability at 6 months) was observed in 10 patients (50%: 6 in arm A, 4 in arm B). Consequently, according to the Fleming design, both treatment regimens were considered to show activity in this disease. Nine patients showed improvement in ADLs (Barthel index), and 6 of these improved by 1 point on the RS. Four died prior to the 6-month study end point and were classified as treatment failures. Three patients died from neurological deterioration, and 1 patient from oncological complications. A fifth patient died of pneumonia and sepsis 14 months after enrollment.

Improvements in disability were typically mild but were functionally important. Two patients with cerebellar ataxia who could not stand without assistance regained the ability to ambulate with a walker. Two patients with pain and incoordination due to sensory neuropathy of the upper extremities noted a reduction in pain and improved ability to manipulate objects. Two patients with limbic encephalitis were able to return to work but still had memory impairment and still required anticonvulsant therapy. Most of the patients who improved participated in structured rehabilitation programs during the study period.

Twice as many patients in arm A experienced improvement in disability compared to arm B (Table 3), although this difference was not statistically significant. Among patients that improved, the majority stabilized during the first 2 months of treatment and then improved gradually over the remainder of the study period. Only 1 patient (Patient A-6, Table 2) showed an acute improvement associated with PLEX. In her case, treatment was started 12 days after onset of ataxia. Three months after PLEX, she experienced a partial relapse while on cyclophosphamide but stabilized at a level that was still improved compared to the initial evaluation. None of the patients in arm B improved with PLEX prior to starting chemotherapy.

Treatment Tolerance and Toxicity

Four of the 20 patients were unable to complete the planned course of 5 PLEX treatments. One patient died of neurological progression after the fourth exchange. One developed a central line infection, and 2 patients experienced episodes of significant hypotension during PLEX. There were no long-term sequelae of these latter complications.

Table 3. Summary of trial by treatment arm

	Arm A	Arm B
Number of patients	10	10
Median age (mean)	65.5 (62.7)	58.5 (58.0)
Sex (M:F)	3:7	2:8
Median symptom duration (range)	3.2 months (0.5–9.5)	3.0 months (1–7.5)
Mean initial Rankin score	3.2	3.8
Mean initial Barthel index	67.5	56.5
Stability or improvement	60%	40%
Improvement	60%	30%
Number alive	7	7
Median follow-up, months (range)	31 (24–41)	27 (23–34)

In arm A, 6 of the 10 patients were unable to complete the planned 6-month course of oral cyclophosphamide. One patient died of neurological progression prior to starting cyclophosphamide. Four developed severe leukopenia (grade 3 or 4) that persisted despite dose reduction. White blood cell count recovered in all cases. Two of these 4 were worsening neurologically and were subsequently treated with oral mycophenolate mofetil without benefit. Another patient experienced severe nausea and vomiting, even on a reduced dose of oral cyclophosphamide. This latter patient was continued on monthly intravenous infusions of cyclophosphamide but did not respond. Overall, cyclophosphamide-related hematologic toxicity was common. Among the 9 patients who took the drug, all developed mild anemia (grade 1 or 2); 3 developed significant lymphopenia (grade 3), and 3 developed severe neutropenia (grade 3 or 4). One patient developed mild hemorrhagic cystitis that resolved after vigorous oral hydration.

Typical side effects of chemotherapy were noted among patients in arm B, but none of the patients discontinued chemotherapy due to toxicity. However, one patient in arm B died of neurological progression prior to starting chemotherapy.

Secondary Outcomes

Six of the patients in arm B obtained a cancer remission. Because most patients achieved or remained in cancer remission and many had good neurological outcome, overall survival in this study is better than that reported in other long-term studies. At the time of this analysis, with follow-up ranging from 23 to 41 months (median = 29 months), 14 (70%) of the 20 patients are still alive. Estimated 12-month survival is 74.7% compared to 33% to 47% in other series (Graus et al., 2001; Keime-Guibert et al., 2000; Sillevis Smitt et al., 2002; Uchuya et al., 1996).

Follow-up paraneoplastic antibody data were available for 12 of the 17 patients who were initially seropositive. In 8, the serum antibody titer decreased (5 were clinically improved, and 3 had worsened). Two patients had stable antibody titers (both had improved). Two patients showed an increase in antibody titer (both had deteriorated neurologically).

Factors Associated with Outcome

We examined several initial patient characteristics as possible predictors of neurological outcome (Table 4). Surprisingly, the duration of neurological symptoms prior to initiation of treatment was not associated with outcome. Patients who improved with treatment tended to be younger and had less initial disability. Only 2 of the 11 nonambulatory patients (RS = 4) improved while 7 of 9 patients who were ambulatory at the time of enrollment (RS < 4) improved (Fisher exact test; $P = 0.02$). Patients with PCA-1 antibodies had a lower frequency of neurological improvement (27%) than patients with other antibodies (71%), but this association was not statistically significant (Fisher exact test; $P = 0.14$). Similarly, patients with cerebrospinal fluid pleocytosis (n = 8; range of cerebrospinal fluid nucleated cell count, 7–57) had lower frequency of response (25%) compared to those without pleocytosis (67%; n = 6; $P = 0.28$).

Discussion

An accurate assessment of treatment efficacy for paraneoplastic neurological disorders is difficult due to the heterogeneity of clinical presentation and the low incidence of these disorders. This study demonstrates the feasibility of evaluating treatment using a prospective design with predefined study end points. We also used a study design to assess the effects of cancer treatment (chemotherapy) independently from an immunosuppressive treatment (cyclophosphamide) in patients without active cancer.

The overall rate of improvement in this study (45%) is better than that reported in previous case studies, and neurological improvement was sustained in our patients after discontinuing treatment. Patients enrolled in this study had clinical features of well-recognized paraneoplastic syndromes with typical cancer and antibody associations. In addition to the actual treatment protocol, there are several possible explanations for our favorable results. First, our study included a group of patients without active malignancy (arm A), and it is possible that autoimmunity is more easily controlled in such patients. Second, we excluded severely disabled patients (RS = 5) and those who had experienced symptoms for longer than 12 months, since previous data suggests these patients are likely to have irreversible deficits. Our data indicate that treatment is most likely to benefit patients with less disability, particularly those who are still ambulatory. These patients have less permanent neuronal loss and therefore have a better substrate for participating in rehabilitation. Contrary to our expectations, the duration of neurological symptoms prior to initiation of treatment did not predict outcome. Since patients with more severe disability tend to be diagnosed earlier than those with less disability (Graus et al., 2001), patients with rap-

Table 4. Baseline predictors of outcome

	Stable/Improved	Worse	*P*-value
Number of patients	10	10	
Sex (M:F)	3:7	2:8	1.0†
Age (years)			
median	56	65.5	0.10*
range	36–78	53–74	
Sx duration‡ (days)			
median	132	59	0.58*
range	11–303	23–265	
Initial Barthel index			
median	85	50	0.09*
range	25–95	25–95	

† Fisher exact test.

* Nonparametric rank sum test.

‡ Duration of neurological symptoms at time of enrollment.

idly progressive, severe disease may have poor outcome despite early treatment. A much larger study would be needed to separate the effects of symptom duration and initial disability on treatment response.

With our study design, it is difficult to determine which component of the treatment protocol was principally responsible for the favorable outcome. While PLEX was clearly beneficial in one case, no other patient showed a clear response to PLEX. Based on the time course of the improvement, our conclusion is that immunosuppression or effective cancer chemotherapy serves to arrest disease progression. Once stable, patients who are still ambulatory have the potential to improve with rehabilitation.

The only other group to conduct a prospective treatment trial for paraneoplastic disorders also reported a favorable outcome, a 75% success rate using immunoadsorption therapy (Batchelor et al., 1998). However, in that study, none of the 13 patients were seropositive for typical neuronal nuclear or cytoplasmic paraneoplastic antibodies, and validated quantitative measures of neurological disability were not used. Nevertheless, these 2 prospective studies together suggest that immunomodulatory therapy in the appropriate patients can improve outcome as compared to the natural course of the disease.

Typically, paraneoplastic neurological disorders present in the context of a malignant neoplasm. Early diagnosis and successful treatment of the underlying malignancy remains critical for survival and for neurological improvement. In our clinical protocol, patients underwent an expedited intensive search for malignancy and prompt institution of chemotherapy. Six patients achieved cancer remission with chemotherapy (arm B), and none of these have shown recurrence during follow-up. Neurological stabilization or improvement occurred in 40% of patients in treatment arm B. Neurological improvement may relate both to elimination of the neoplasm as a stimulus for neurological autoimmunity and to direct immunosuppressive effects of the chemotherapeutic agents. Even though patients with paraneoplastic neurological disorders are often disabled and their tumors are limited in stage, effective cancer treatment should be initiated promptly to provide the best chance for neurological stabilization or recovery. Ultimately, treatment of the underlying tumor combined with chronic immunosuppression may offer the best chance of arresting neurological progression.

Identification and eradication of the underlying malignancy is considered the optimal treatment for paraneoplastic neurological disorders. The treatment of patients without evidence of active malignancy has been uncertain, and no previous studies have specifically addressed treatment in this group of patients. Our study demonstrates that such patients treated with aggressive immunosuppression can achieve a rate of neurological response similar to those whose who receive chemotherapy for their malignancy. We used a continuous oral immunosuppressive regimen that was dosed to produce mild to moderate bone marrow suppression. This level of immunosuppression was not well tolerated by some patients, but all 4 patients who tolerated the treatment experienced sustained neurological improvement. Several continued on oral cyclophosphamide after completion of the study because of continuing improvement. Patients need close oncological follow-up since impairment of cellular immunity has the potential to impair immune surveillance for malignancy. In our study, however, only 1 patient in arm A developed a cancer recurrence, and this occurred 5 months after stopping cyclophosphamide.

Further prospective trials are needed, particularly studies of better tolerated immunosuppressive agents with specific activity against cellular autoimmunity. Early diagnosis, arrest of neurological progression, and durable improvement in disability are the ultimate goals.

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